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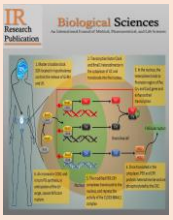

Process Validation of Metformin Hydrochloride Tablet (500 mg) according to USFDA

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ABSTRACT

Metformin hydrochloride is an oral anti-diabetic drug from the biguanide class used mainly to treat type 2 diabetes mellitus. As per ISO 17025, Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled. This research aimed to study prospective process validation for Metformin Hydrochloride 500 mg tablet dosage formulation. One initial process validation with a batch size of 200 tablets was performed. Furthermore, method, equipment, and validation criteria were taken. The critical parameter involved in sifting, blending, and compression stages were identified and evaluated as per the validation master plan. The outcome indicated that this process validation data provides a high degree of assurance that the manufacturing process produces products meeting its predetermined specifications and quality attributes.

Introduction

As per ISO 17025 Validation is the confirmation by examination and the provision of objective evidence that the particular requirements for a specific intended use are fulfilled [1-3]. As per USFDA (1987) "Process validation is establishing documented evidence which provides a high degree of assurance

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that a specific process (such as the manufacturing of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics." As per USFDA (2008) "Process validation is the collection and evaluation of data, from the process design stage throughout the production, which establish scientific evidence that a process is capable of consistently delivering quality products." The principal elements of validation include documented evidence, high degree of assurance, specific process, consistency, and predetermined specifications. There are different types of validations [4], including Prospective validation: establishes documented evidence prior to process implementation that a system does what it proposed to do based on pre-planned protocols; Retrospective validation: involves the examination of past experience of procedures, and equipment remain unchanged; production on the assumption that composition, such experience and the results

of in-process and final control tests are then evaluated; Concurrent validation: establishes documented evidence that a process does what it purports to do, based on information generated during actual implementation of the process; Revalidation: repeats the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems.

Metformin hydrochloride is an oral anti-diabetic drug from the biguanide class used mainly to treat type 2 diabetes mellitus [5]. Evidences suggest that insulin resistance and resulting hyper insulinaemia play a central role in the pathogenesis of the syndrome. Metformin, an insulin sensitizer, not only improves hyperandrogenism but also improves ovulation as well as pregnancy rates in patients with PCOS, non-alcoholic fatty liver disease (NAFLD) and premature puberty [6]. Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of N, N dimethyl-guanidine free user [7]. French physician Jean Sterne published the first clinical trial of Metformin as a treatment for diabetes. It was introduced to the United Kingdom in 1958, Canada in 1972, and the United States in 1995 [8,9].

Drug products that are bio-pharmaceutically and chemically equivalent must be identical in their quality, strength, purity and active ingredient release profile. They must to be in the same dosage form and intended for the same route of administration [10]. Dissolution testing of drug product is an important criterion in assessing the quality control to monitor batch to batch consistency of drug release [11]. The variations in the drug release among some generics indicate deficiency in the entire drug formulation and the delivery system. Dissolution rate determination used also for prediction of in-vivo bioavailability in most oral preparations [12,13].

Manufacturing methods and the excipients used in the production processes could contribute to the quality and release skilfulness of medicament. Therefore, to ensure the requisite quality, drug manufacturers are required to examine their products during and after manufacturing and at various intervals during the shelf life of the product [14].

Materials and Methods

Materials

Metformin HCl was gifted by La Pharma, Ludhiana, Punjab, India, Lactose Monohydrate and Disodium Hydrogen Phosphate was purchased from CDH Fine chemicals Ltd., Starch IP and Hydrochloric Acid was purchased from Loba Chemie Private Limited, Maharashtra, India., Talc, Magnesium Stearate, Potassium Dihydrogen Phosphate and MCC was purchased from Hi media laboratories Private Limited Mumbai, India.

Pre-formulation Studies of Metformin HCl

Pre-formulation studies are indispensable protocol for development of safe, effective and stable dosage form. Thus, in order to ensure optimum condition for clinically beneficial delivery system, pre-formulation studies were carried out. Pre-formulation parameters conducted are shown in Figure 1 were performed to get the preliminary information about procured Metformin HCl.

Physical appearance

The physical appearance of the drug was checked by visual observation, dispersing the drug on clean butter paper. The observations showed it was a white crystalline powder.

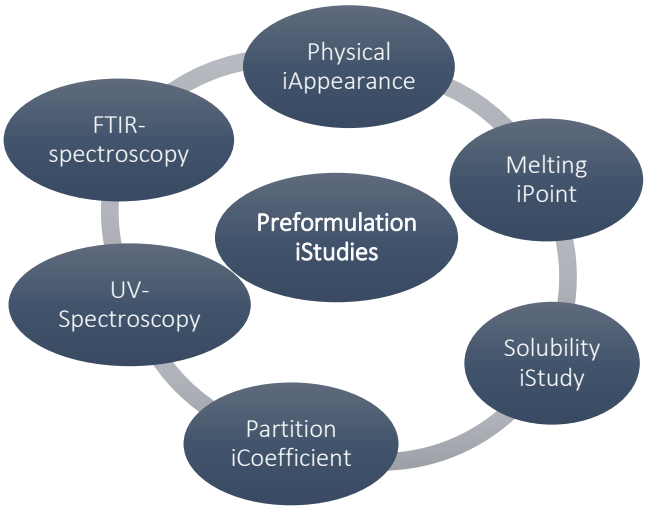

Figure 1. Pre-formulation Studies Parameters

Melting Point

Melting point of Metformin HCl was considered as a criterion for purity as well as for identification. Capillary melting point apparatus was used to determine melting point of Metformin HCl. Small

amount of Metformin HCl was filled in the capillary and melting point was observed [15].

Solubility study

Solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Metformin hydrochloride, 2.0 g is soluble in 20mL of water and is freely soluble in water, slightly soluble in alcohol and insoluble in acetone and in methyl chloride, as per Indian Pharmacopoeia (2018), the solubility of Metformin HCl was tested in various solvents. A definite quantity (1 mg) of drug was dissolved in 10ml of each investigated solvent at room temperature. The solubility was observed only visually.

Partition Coefficient

Partition coefficient studies were performed by taking 10 mg of Metformin HCl which was further was added to 50:50 ml mixture of distilled water: n-octanol. It was shaken separately for half an hour. Both phases were taken together in a separating funnel and shaken for 4 hours on a mechanical shaker. Allowed to stand long enough for the phase separation [16]. After the phase separation, water was collected and readings was taken at 233 nm. Partition coefficient was evaluated as -

$$\log p = \frac{\text{Amount of drug in organic phase (octanol)}}{\text{Amount of drug in aqueous phase (water)}}$$

Fourier transformed infra-red Spectroscopy Studies

IR spectra were recorded for identification and to check purity of procured Metformin HCl. Sample 2 % (w/w) was mixed in dry KBr. The mixture was ground into a fine powder using mortar/pestle before compressing into KBr disc under a hydraulic press at 10,000 psi. Each KBr disc was scanned 32 times at 4 mm /sec.at a resolution of 2 cm-1. The characteristic bands for compound were [17].

UV Spectroscopy Analysis

- *Determination of λmax for Metformin HCl*

For the determination of λmax, 10 µg/ml concentration of Metformin HCl were prepared in methanol. The prepared solutions were scanned using UV-Spectrophotometer in the range 200 to 400nm. The wavelength showing maximum absorbance was selected (I.P. 2014)

- *Calibration Curves Studies in Methanol*

The calibration curve standard solutions were prepared of concentration 5.0, 10.0, 15.0, 20.0, 25.0, and 30.0 µg/ml in duplicate. Baseline correction with blank was done before taking spectra. The absorbance was measured at λmax233 nm of Metformin HCl in same solvent mixture against blank solution using UV spectrophotometer. The mean absorbance was measured and a graph was plotted between concentration (x-axis) and absorbance (y-axis). The line equation and correlation coefficient were calculated for the calibration curve.

- *Calibration curve of Metformin HCL in PBS 6.8*

Stock solution of 1mg/ml of Metformin HCL was freshly prepared by dissolving 10mg of pure drug in 10ml of PBS. Prepared solution was further diluted with PBS (6.8 pH) to obtain concentration of 100 µg/ml. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 ml were withdrawn from the stock solution and place separately in different 10 ml volumetric flasks and volume was made up to 10 ml with methanol to obtain working solutions 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/ml. Absorbance of all the solutions were recorded at λmax 233 nm against blank using UV-visible spectrophotometer.

- *Calibration curve of Metformin HCL in 0.1N HCL*

Stock solution of 1mg/ml of Metformin HCL was freshly prepared by dissolving 10mg of pure drug in 10ml of 0.1N HCL. Prepared solution was further diluted with 0.1N HCL to obtain concentration of 100 µg/ml. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml were withdrawn from the stock solution and place separately in different 10 ml volumetric flasks and volume was made up to 10 ml with 0.1N HCL to obtain working solutions 5, 10, 15, 20, 25, and 30 µg/ml. Absorbance of all the solutions were recorded at λmax 233 nm against blank using UV-visible spectrophotometer.

- *Calibration curve of Metformin HCL in Distilled Water*

Stock solution of 100 µg/ml of Metformin HCL was freshly prepared by dissolving 10mg of pure drug diluted with 2 ml of methanol and 98 ml of distilled water. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 ml were withdrawn from the stock solution and

place separately in different 10 ml volumetric flasks and volume was made up to 10 ml with distilled water to obtain working solutions 5, 10, 15, 20, 25, 30, and 35 µg/ml. Absorbance of all the solutions were recorded at λmax 233 nm against blank using UV-visible spectrophotometer.

Formulation of Metformin HCl Tablet using Wet Granulation Method

Ingredients used in the Formulation are shown in Table 1. All ingredients were passed through 40 mesh size to get uniform size particle and weighed accurately. The drug and all additives were mixed in a pestle mortar. The 10% solution of PVP in 100 ml isopropyl alcohol was prepared. It was used as a binding solution. The granules were prepared by wet granulation method, using PVP as a binding agent. The granules were dried in hot air oven at 70° C for 10 minutes. Talc and magnesium stearate were added as lubricants. The tablets were punched using single punch hand operated tablet punching machine.

Table 1. Formulation of Metformin HCL Tablets

S. No.	Ingredients	Quantity in mg/ Tablet	Quantity required/Batch of 200 tablets (g)
1	Metformin HCl	500	100
2	PVP K30	50	10
3	Lactose Monohydrate	12.5	2.5
4	MCC	72.5	14.5
5	Magnesium stearate	7.5	1.5
6	Talc	7.5	1.5
7	Total	**650**	**130**

Pre compression studies of Metformin HCl

Bulk Density

Bulk density is defined as ratio of total mass of granules to the bulk volume of granules. It was measured by pouring initially weighed granules into measuring cylinder (10 ml) and noted down the volume (bulk volume), it is expressed in g/ml. It was calculated as per the equation [18].

$$\mathbf{Db} = \frac{\mathbf{M}}{\mathbf{Vb}}$$

Where, M = granules mass, Db= bulk density and Vb = granules bulk volume.

Tapped Density

Tap density was calculated in same way as bulk density, volume of the granules was noted after 500 tapping from 1.5-inch height. It was calculated using the equation [18].

$$\mathbf{Dt} = \frac{\mathbf{M}}{\mathbf{Vt}}$$

Where Dt = Tapped density,Vt = tapped volume, M = granules mass

Angle of repose

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The granules was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius of the base of the conical pile was measured. The angle of repose (θ) was calculated as per equation [19].

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ = Angle of repose, h = Height of the cone, r = Radius of the cone base.

Carr's Index

The 'Compressibility index' (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. Table 2 shows the compressibility index values and relative flow property. These differences are reflected in the Carr's index which is calculated as per the equation [19]

$$\textbf{Compressibility Index} = [(\boldsymbol{\rho tap} - \boldsymbol{\rho b}) / \boldsymbol{\rho tap}] / \times \mathbf{100}$$

Where, ρb= bulk density and ρtap= tapped density

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by following equation [19].

Hausner's Ratio=Tapped density (ρtap) / Bulk density (ρb)

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 exhibits poor flow.

Post compression parameter study of Metformin HCL

Thickness

The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated [20]. It is expressed in mm.

Table 2. Flow Properties Index

Angle of Repose (°)	Compressibility index	Hausner's Ratio	Flow Properties
25-30	≤10	1.2-1.3	Excellent flow
31-35	11 – 15	1.3-1.4	Good flow
36-40	16-20	1.4-1.5	Fair flow
41-45	21-25	1.5-1.6	Passable flow

Hardness

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto Hardness Tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured [21]. The value at this point was noted.

Friability

Friability is the measure of tablet strength. Roche Friability or was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed 6 tablets was placed in Roche friability or which was then operated for 100 revolutions i.e., 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable [20]. Percent friability (% F) was calculated as follows

$$\mathbf{F} = \frac{\boldsymbol{Initial\ weight - Final\ weight}}{\mathbf{Initial\ weight}} \times \mathbf{100}$$

Weight variation test

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. (Indian pharmacopoeia,1996).

Drug Content

Ten tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 100 mg of Metformin HCl was weighed and dissolved in 100 ml of phosphate buffer (pH 6.8). This was the stock solution from which 0.1 ml sample was withdrawn and diluted to 10 ml with phosphate buffer, dilutions were prepared in triplets. The absorbance was measured at wavelength 233 nm using double beam UV-Visible spectrophotometer [22]. Drug content was calculated using formula.

% Purity = 10 C (Au / As)

Where, C - Concentration,

Au and As - Absorbance's obtained from unknown preparation and standard Preparation respectively.

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the water maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded [23].

Critical Quality Attributes

Blend Uniformity Monitoring

Blending is one of the most critical steps in the production process of solid dosage forms. The process has become even more critical since the discovery of very potent drugs, with a Blend homogeneity is crucial to ensure content uniformity in the end product, especially in a direct compression process where blending is the only step prior to compression. For the interpretation of the spectral information collected during blending several methods have been tested, most based on comparing blend spectra directly or indirectly with spectra of pure compounds [20]. Differences between spectra or values derived from spectra are quantified and used as a function of blend homogeneity with the limitation of defining the ideal spectrum.

Disintegration time

The time required for in-vitro disintegration of six tablets, placed in each tube of disintegration test apparatus, was measured at 37±2°C using 900 ml distilled water.

In vitro dissolution studies

Tablet dissolution was assessed using standard USP dissolution apparatus type II (Table 2). The dissolution media used was 900ml of 0.68% w/v solution of potassium dihydrogen phosphate, adjusted to pH 6.8 by addition of 1M sodium hydroxide. The temperature was maintained at 37 ± 0.5°C. At predetermined time intervals, an aliquot of 10 ml sample was withdrawn, and made up to 10 ml with dissolution media. Then these samples were measured in UV at 233 nm.

Table 3. Dissolution parameters

Apparatus	USP II, Basket
Medium	Phosphate buffer solution pH 6.8
Medium volume	900ml
Medium Temp.	37±0.5° C
Paddle speed	100 rpm
Sampling Time	15, 30, 45 Min
Sampling Volume (ml)	10 ml
Absorbance nm	233

Process Validation of Metformin Hydrochloride Tablets

Dry Mixing and Granulation

Equipment used: Rapid Mixer Granulator.
Size/capacity: 1.5 L
Mixing time: 5 minutes
Ingredients after sifting is loaded into the Rapid Mixer Granulator and is dry mixed for 5minutes. Sampling is done at 5 different places and is sent for Assaying. Starch paste is added during mixing of the ingredients till desired granular mass is obtained.

Drying

Equipment used: Fluidized bed drier
Drying temperature: 40 °C
The granular mass is loaded in the FBD. Dry the granules till LOD attains between 2-3.5%w/w. Sampling is done at 3 different time intervals each of 3gms.

Blending and lubrication

Equipment used: Octagonal Blender
Run time: 5, 10, 15, 20 min
Load the dried granules into the octagonal blender and blend it for 10 minutes. Lubricate the above for 5 minutes. Sampling is done at 5 different places after the completion of the lubrication and the samples are analyzed for content uniformity, bulk density, particle size distribution.

Tablet Compression

Equipment used: Compression machine
Size: 8 mm
Shape: Round
Dies description: flat and plain
Run the tablet compression machine at minimum speed (25 RPM) and sampling is done when the powder level in the hopper is maximum and minimum and is sent for the QC analysis.

Quality tests

Description, Uniformity of Weight, Thickness, Diameter, Hardness, Friability, Disintegration Time.
Run the tablet compression machine at maximum speed (33RPM) and samplings is done, when the powder level in the hopper is maximum and minimum and samples are analyzed. Furthermore, Description, Thickness, Diameter, Hardness, Friability, Disintegration Time. Sampling is done at various settings and speeds from the hopper at the compression stage.

Results and Discussion

Physical Appearance

Metformin Hydrochloride was white crystalline powder, odourless and has bitter taste.

Melting Point

The melting point determination was performed to check the purity of drug. The melting point of the Metformin HCL was found to the range 223-224˚C, which complies with the standard i.e., 223-226˚C.

Solubility Determination

Solubility was determined by saturation solubility method. An excess amount of drug was added in each of the dissolution media or water at room temperature with occasional stirring. The solution was filtered after 24 hours and amount of drug dissolved was determined using UV Spectrophotometer (Table 4).

Partition Coefficient

Table 4. Solubility of Metformin HCl

Medium	Solubility (mg/ ml)
Water	321
0.1 N HCl	329
PBS (6.8 pH)	326
Methanol	Freely Soluble

The result obtained for log P oct/wat was -1.20. Data obtained from partition coefficient determination suggest that Metformin HCl was hydrophilic in nature.

FTIR Spectroscopy

Infrared spectrum gives information about the functional groups present in the compound. FTIR spectrum of Metformin HCl was recorded and found to be in compliance with the various specific peaks for Metformin HCl. The FTIR spectrum is given in the Figure 2. The wave number values for each peak have been explained in Table 5.

All the tests of the identification studies were found to be in compliance with the data available in the literature. Thus, it is confirmed from these results that the procured drug Metformin HCl was free from impurities.

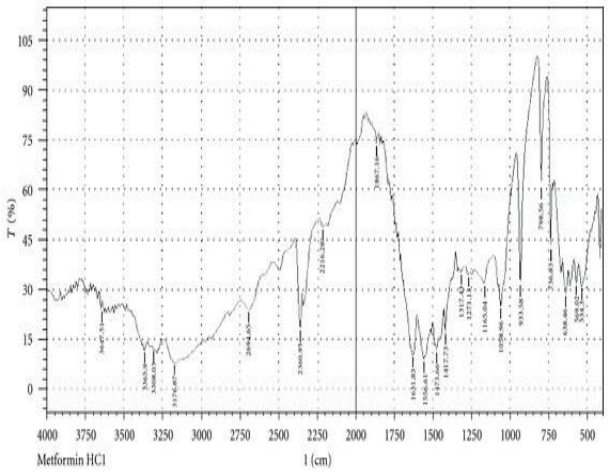

Figure 2. FTIR spectra of Pure Metformin Hydrochloride

Standard Curve of Metformin HCl

Figure No. 3.2 represent linearity range and calibration curve of Metformin HCL in methanol at λ max 233nm. Estimation of Metformin HCl in solution was done using UV spectrophotometric method. The R^2 value and the slope was found to be 0.997 and y = 0.033x + 0.014 respectively.

Table 5. Interpretation of FTIR Spectral data for Metformin HCl

Observe number (cm^{-1})	Characteristic wave number range (cm^{-1})	Functional group
3372	3500-3000 cm-1	(C-H) Stretching
3295	3600-3200 cm-1	(N-H) Stretching
3174	3200-3000 cm-1	(C–H) Stretching
2692	3000-2500 cm-1	(O-H) Stretching
2214	2500-2000 cm-1	(C≡C) Stretching
1416	1500-1000 cm-1	(C-N) Stretching

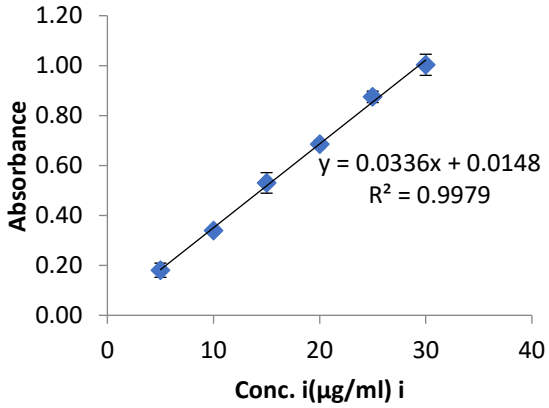

Figure 3. Standard Curve of Metformin HCL in Methanol

Standard Curve of Metformin HCL in Phosphate buffer (pH 6.8)

Figure 4 represent linearity range and calibration curve of Metformin HCl in phosphate buffer (pH 6.8) at λ max 233nm. Estimation of Metformin HCl in solution was done using UV spectrophotometric method. The R² value and the slope was found to be 0.997 and y = 0.016x + 0.102 respectively.

Standard Curve of Metformin HCl in 0.1 N HCl

Figure 5 represent linearity range and calibration curve of Metformin HCL in 0.1N HCl at λ max 233nm. Estimation of Metformin HCl in solution was done using UV Spectrophotometric method. The R² value and the slope was found to be 0.994 and y = 0.027x - 0.043 respectively.

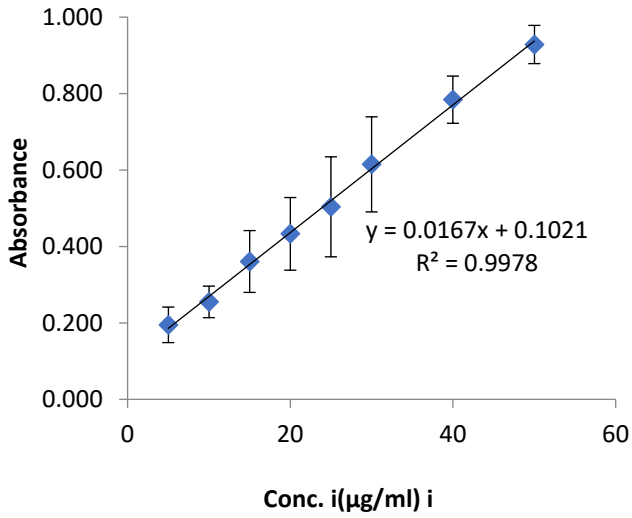

Figure 4. Standard Curve of Metformin HCl in Phosphate buffer (pH 6.8)

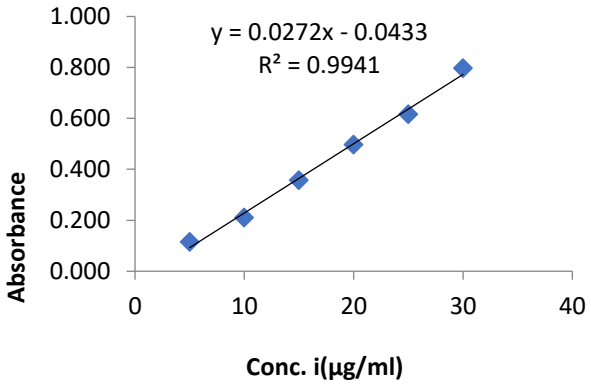

Figure 5. Standard Curve of Metformin HCl in 0.1 N HCl

Standard Curve of Metformin HCl in Distilled water

Figure 6 represent linearity range and calibration curve of Metformin HCl in distilled water at λ max 233nm. Estimation of Metformin HCl in solution was done using UV spectrophotometric method. The R² value and the slope was found to be 0.995 and y = 0.027x + 0.007 respectively.

Angle of repose

Angle of repose of Metformin Hydrochloride granules were found to be 32.21 indicated the good flow. Angle of repose result are showing 30-35 indicating the good flow behaviour.

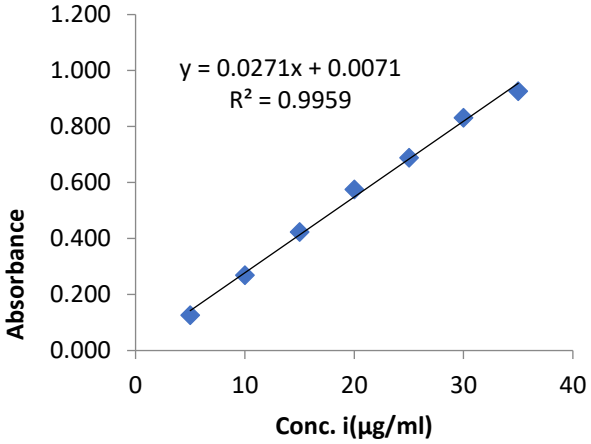

Figure 6. Standard Curve of Metformin HCl in Distilled water

Bulk Density and Tapped Density

Bulk density of Metformin HCl granules found to be 0.60 and taped density of Metformin HCl granules were found to be 0.82.

Hausner's ratio

The hausner's ratio of Metformin Hydrochloride tablet were found to be 1.18 i.e. good. The hausner's ratio between 1.12-1.18 indicated the excellent flow.

Carr's index

Carr's index of Metformin Hydrochloride granules were found to be 11.60 that indicating the good.

Blending

Blending was performed in octagonal blender, the blending parameters are shown in the Table no. 3.8. Blend samples was taken from 5 different locations from blender at 5, 10, 15 & 20 minutes interval, and it was found that after 20 minutes of blending the Metformin was uniformly mixed with the excipients with the standard deviation of 0.013, means 1.3% and it is in acceptable range, the results of assay are shown in Table 6 and Figure 7.

Table 6. Assay of Blend for content uniformity

Location	Assay of Blend at Different Time Intervals			
	5 min	**10 min**	**15 min**	**20 min**
Top left	98.30%	117.30%	96.20%	99.20%
Top right	135.30%	96.80%	98.10%	98.10%
Centre	113%	101.80%	118.80%	101.80%
Bottom left	81.50%	98.20%	105.10%	100.70%
Bottom right	50.80%	92.60%	95.80%	98.50%
Mean	95.78%	101.34%	102.80%	99.66%
Standard Deviation	0.286 (28.60%)	0.085 (8.50%)	0.086 (8.60%)	0.013 (1.30%)

Compression process

The blend obtained was run on the RIMEK MNI PRESS II compression machine. The Speed of compression in RPM was optimized and the tablets was tested for various parameters like description, average weight, uniformity of weight, thickness, hardness, friability, disintegration time and dissolution to assure the reproducibility of the compressed tablets. The compression was run on different RPM (15, 30, 60) and the tablet formulated were tested on different parameters like description, average weight, uniformity of weight, thickness, hardness, friability, disintegration time and dissolution to assure the reproducibility of the compressed tablets. The concluded data of different batches formulated at different RPMs are given below in Table 7 and Figure 8. All the results were in the acceptable range

Finished product analysis

On the behalf of all three stages data, it was concluded that at 30 RPM the batch is having optimum results. So a final batch was formulated at 30 RPM on the basis of previous data and its parameters were tested for various parameters like description, average weight, uniformity of weight, thickness, hardness, friability, disintegration time and dissolution to assure the reproducibility of the compressed tablets. The results of tested parameters are given in Table 8 and Figure 9. In final batch, it was concluded that the final batch was having analysis results in acceptable range with White, round, uncoated tablets and plain on both side appearance, average weight of 654.9 mg,

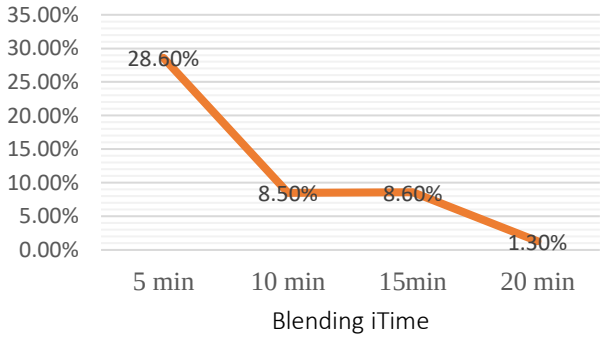

Figure 7. Assay of blend of Metformin

Table 7. Different Stages of the Compression Process

Parameters	Observation			Acceptance Criteria
Machine speed	15 RPM	30 RPM	60 RPM	To be recorded
Description	White, round, uncoated tablets, plain on both sides.	White, round, uncoated tablets, plain on both sides.	White, round, uncoated tablets, plain on both sides.	White to off white, round, uncoated tablets plain on both sides.
Uniformity of weight (mg)	L – 645.6 H –684.2	L – 641.4 H – 673.2	L - 630.8 H - 671.5	663 ± 5% (628-694)
Hardness (N/m)	4.5 kg/cm²	4.6 kg/cm²	4.8kg/cm²	3-6 kg/cm²
Thickness (mm)	4 mm	4mm	4mm	3.80 mm ±0.20 mm (3.60 mm to 4.00 mm)
Disintegration time (min)	6 min 50 sec	6 min 40 sec	6 min 45 sec	NMT 15 minutes
Friability (%w/w)	0.12	0.11	0.11%	NMT 1.0 % w/w (Weight: around 6.5 g)
Dissolution (%)	Min:87 Max:95 Avg:91	Min:88 Max:96 Avg:92	Min:82 Max:92 Avg:87	Not less than 80 (Q) in 30 Minute

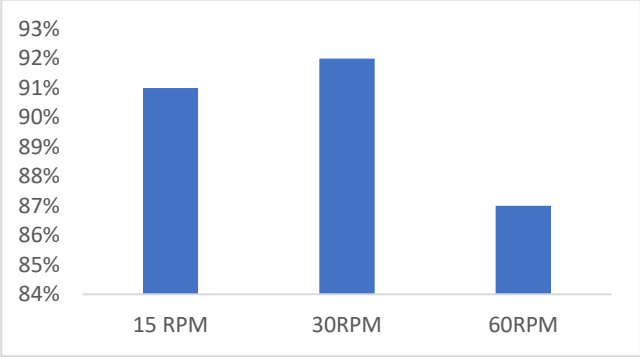

Figure 8. Release profile of Metformin tablet at different stages

hardness 4.6 kg/cm², Disintegration time 6 min 55 sec, average dissolution profile 98% and Assay of 101.3%.

Conclusion

The outcome indicated that this process validation data provides a high degree of assurance that the manufacturing process produces products meeting its predetermined specifications and quality attributes.

Table 8. The final batch formulated at 30 RPM

Tests	Observations	Acceptance Criteria
Machine speed	30 RPM	To be recorded
Description	White, round, uncoated tablets, plain on both side	White to off white. round, uncoated tablets plain on both sides.
Average weight (mg)	654.9 mg	654.9±5% (622.15-687.64 mg)
Tablet Hardness	4.6 kg/cm²	3-6 kg/cm²
Loss on drying	1.2 %	Not more than 5.0%
Disintegration time	6 min 55 sec	NMT 15 minutes
Dissolution (% Release at 45 min)	Min. 95 %; Max. 101%; Mean: 98 %	Not less than 80% in 30 minutes.
Assay	101.3 %	95.0 % to 105.0% of label claim.

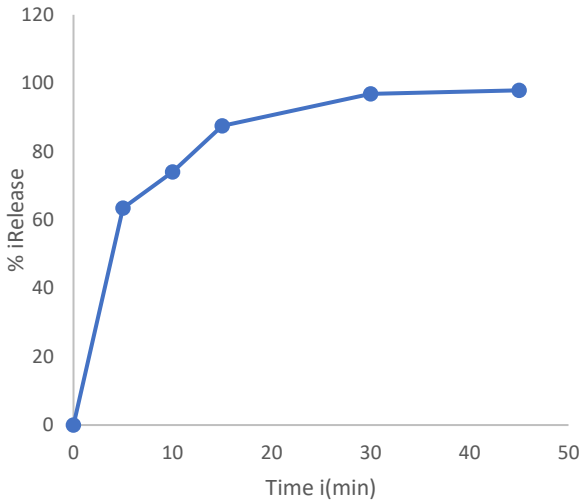

Figure 9. Release profile of Metformin Tablet

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Conflict of interest

Nil

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